Indianapolis, IN) with 30 cycles of 35 seconds at 95°C, 35 seconds at 60°C, and 35 seconds at 72°C using a MJ thermocycler (MJ Research, Watertown, MA). For the AHAS621 target, primers common to both AHAS108 and AHAS109 were designed with the following sequences: 5'GCAGTGGGACAGGTTCTAT (PHN21971) (SEQ ID NO: 16) and 5'AGTCCTGCCATCACCATCCA (PHN21972) (SEQ ID NO: 17). For the AHAS165 target, the following primers were used: 5'ACCCGCTCCCCCGTCAT (PHN21973) (SEQ ID NO: 18) and 5'ATCTGCTGCTGGATGTCCTTGG (PHN21974) (SEQ ID NO: 19). For the moPAT/GFPm target, primers used were: 5'CGCAACGCCTACGACTGGA (PHN21976) (SEQ ID NO: 20) and 5'TGATGCCGTTCTTCTGCTTGTC (PHN21978) (SEQ ID NO: 21). PCR fragments were purified and either cloned (see below) or directly sequenced in both directions on an ABI 377 automated sequencer.

In the Claims

Please cancel claims 1 and 10 without prejudice or disclaimer.

Please amend the claims as follows:

2. (Amended) The chimeric oligonucleotide of claim 6, wherein said chimeric oligonucleotide comprises at least one region of contiguous unpaired bases disposed so that the unpaired region separates the chimeric oligonucleotide into a first and a second strand.

3. (Amended) The chimeric oligonucleotide of claim 2, wherein said first and said second blocks of RNA residues are comprised of a 2'-O or 2'-OMe ribose.

4. (Amended) The chimeric oligonucleotide of claim 2, wherein said first and said second blocks of RNA residues comprise at least 5 contiguous nucleotides.

5. (Amended) The chimeric oligonucleotide of claim 3, wherein said block of DNA residues comprises at least 5 contiguous nucleotides.

6. (Amended) A chimeric oligonucleotide comprising at least a first block of RNA residues and a second block of RNA residues, wherein said first and said second blocks of RNA residues are homologous to a plant herbicide resistance gene and flank a block of DNA residues, said oligonucleotide being capable of folding to form a duplex oligonucleotide.

11. (Amended) The chimeric oligonucleotide of claim 6, wherein said chimeric oligonucleotide is selected from the group consisting of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

Status of the Claims

Claims 1-9 and 11 were rejected. Claim 1 has been cancelled without prejudice or disclaimer. Claim 10 was withdrawn from consideration as being drawn to a non-elected invention and has been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the claims in a continuation or divisional application. Claims 2-9 and 11 are pending in the present application.

Claims 2, 3, 4, 5, 6, and 11 have been amended to more clearly define the invention. Specifically, claims 3, 4, and 6 now recite "at least a first block of RNA residues and a second block of RNA residues." Claims 5 and 6 now recite a "block of DNA residues." Claim 2 has been amended to replace "molecule" with "chimeric oligonucleotide" and now has proper antecedent basis. Claim 11 has been amended and no longer references the figures. Support for these amendments can be found throughout the specification and in the originally filed claims.

Claim 2 has been further amended to alter dependency. Specifically, claim 2 now depends on claim 6.

No new matter has been added by way of these amendments. Reexamination and reconsideration of the claims, as amended, is requested.

Election/Restriction

Claim 10, which was withdrawn from consideration, has been cancelled without prejudice or disclaimer subject to the restriction requirement of September 21, 2001.

Applicants thank the Examiner for the telephone interview of July 19, 2002. The interview clarified that generic claims 1 and 6 are not being treated as linking claims, and, therefore, the restriction of claim 10 will not be withdrawn upon allowance of the generic claims. As there are no linking claims present, claim 10 will not be subject to a statutory provisional and/or non-statutory double patenting rejection over the claims of the instant invention in a subsequent continuation or divisional application. See MPEP 809.03.

Amendments to the Specification

The specification has been amended to correctly reference the SEQ ID NOS present in the sequence listing. No new matter has been added by way of these amendments. Applicants submit the specification is now in compliance with 37 C.F.R. 1.821-1.825.

Amendments to the Sequence Listing

The sequence listing has been amended to include SEQ ID NOS: 14-29. SEQ ID NOS: 14-21 comprise oligonucleotides set forth on pages 17-20 of the specification. SEQ ID NOS: 22-29 are set forth in Figures 1-13 of the specification. No new matter has been added by these additions to the sequence listings.

Amendment to the Priority Claim

The priority claim under 35 U.S.C. § 119(e) has been amended. Specifically, the specification has been amended on page 1, lines 3-4 to claim the benefit under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/098,235, filed August 28, 1998 and U.S. Application Serial No. 60/065,628, filed November 18, 1997.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 1-9 and 11 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

First, the Examiner asserts that it is unclear in claim 1 what the blocks of RNA intervene and which oligonucleotide residues form a duplex. Claim 1 has been cancelled. Related claim 6 has been amended to more clearly define the invention. Specifically, amended claim 6 now recites "at least a first block of RNA residues and a second block of RNA residues." The term "intervening blocks of RNA residues" is no longer recited in the claims. Applicants respectfully submit that the amendment obviates the rejection.

The Examiner further asserts that claim 4 is indefinite because it is unclear which "RNA block" is being described. As noted above, claims 3, 4, and 6 have been amended to have proper antecedent basis and now recite "said first and said second block of RNA residues." Applicants submit that this amendment clarifies which RNA block is being described, and the rejection has been obviated.

The Examiner rejected claim 5 as indefinite for failing to particularly point out which "DNA block" is being described. Claims 5 and 6 have been amended and now recite "a block of DNA residues." Furthermore, the claims refer to only one block of DNA residues that is flanked by a first and a second block of RNA residues. Therefore, Applicants respectfully submit that it is clear what the term "block of DNA residues" describes. The amendment obviates the rejection.

The Examiner asserts that claim 6 is indefinite because it is unclear which "plant nucleotide sequence" is being described. Claim 6 has been amended and recites a "plant herbicide resistance." The amendment has obviated the rejection.

Finally, the Examiner rejected claim 11 as indefinite because it refers to the figures. Claim 11 has been amended to delete reference to the figures and now properly recites the appropriate SEQ ID NOS. The amendment obviates the rejection.

In view of the claim amendments, claims 2-9 and 11 particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Accordingly, the rejection of claims 1-9 and 11 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 1-9 and 11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kmiec *et al.* (U.S. Patent Nos. 5,565,350 and 5,795,972) and Yoon *et al.* (1996) *Proc. Natl. Acad. Sci. 93*:2071-2076 in view of Eichholtz *et al.* (U.S. Patent No. 6,225,114). This rejection is respectfully traversed.

Yoon *et al.* is drawn to targeted gene correction of episomal DNA in *mammalian* cells mediated by a chimeric RNA-DNA oligonucleotide. There is no discussion in the reference for the utilization of chimeric RNA-DNA oligonucleotides to generate a predetermined nucleotide mismatch in a target sequence in the genome of a plant cell. While Yoon *et al.* postulate on page 2075 that it is probable that the gene correction event is mediated by a specific mismatch repair system, there is no suggestion in the reference to utilize the method in plant cells or even speculation to suggest that the repair mechanism would function in plant cells.

Similarly, Kmiec *et al.* ('350 patent) teach methods and compositions directed the use of duplex oligonucleotides for the mutation of particular genes of interest in a fungus (Example 1, column 7) and in a mammalian cell (Example 2, column 8). Specifically, Kmiec *et al.* ('350 patent) teach oligonucleotides directed to making alterations in the ura-3 gene in fungus and in the oncogene H-ras in human NIH 3T3 cells. As with Yoon *et al.*, Kmiec *et al.* ('350 patent) provides no evidence that the chimeric oligonucleotide would be successful in plants, much less do they suggest oligonucleotides designed to introduce mutations in a plant herbicide resistance gene or an EPSPS gene.

Kmiec *et al.* ('972 patent) discloses chimeric oligonucleotide having sequences homologous to a plant gene and suggests the use of these oligonucleotides to introduce specific genetic changes in plant and animal cells. Kmiec *et al.* does not suggest the design of chimeric

oligonucleotides having sequences homologous to plant herbicide resistance genes or EPSPS genes as claims by the instant invention.

And finally, Eichholtz *et al.* ('114 patent) is drawn to nucleic acids encoding glyphosate-resistant EPSPS enzymes. Plants having mutant EPSPS genes are provided. While the '114 patent provides glyphosate resistant plants, these plant lines are produced by the insertion of the entire mutant EPSPS gene into the plant genome. There is no teaching or suggestion to design or use a chimeric oligonucleotide to alter the genome of the plant, much less, to direct a change in a plant herbicide resistance sequences or an integrated or endogenous EPSPS gene.

The Examiner asserts that one of ordinary skill in the art would have been motivated to combine the methods and compositions taught by and Yoon *et al.* and Kmiec *et al.* ('350 patent and '972 patent) with the disclosure by Eichholtz *et al.* ('114 patent) in order to arrive at the claimed invention. Applicants maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The Examiner asserts that the motivation to combine the references is derived from the fact that "one of ordinary skill in the art would have been motivated to utilize such chimeric oligonucleotides for mutagenizing EPSPS because its nucleic acid has been previously disclosed by Eichholtz *et al.*, and EPSPS's role in herbicide resistance has been known and was previously taught in the art by many, including Eichholtz *et al.*" (page 6, lines 13-17, Office Action mailed April 23, 2002). The Examiner's reasoning is insufficient to establish a motivation to combine the cited references. The Federal Circuit has stated "the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fitch*, 972 F.2d 1260, 23 USPQ 2d 1780 (Fed. Cir. 1992).

First, the claims of the present invention are drawn to a chimeric oligonucleotide that contain regions homologous to plant herbicide resistance genes (independent claim 6), EPSPS genes (claims 9 and 11), and genes that confer resistance to sulfonylurea and imidazolinone (claims 7 and 8). The art cited by the Examiner does not suggest to those of ordinary skill that they should make the claimed composition. As acknowledged by the Examiner, the primary

references (Yoon *et al.* and Kmiec *et al.* ('350 patent and '972 patent)) do not suggest the use of the chimeric oligonucleotides to modify herbicide resistance genes or the EPSPS gene. While Kmiec *et al.* ('972) suggest the use of chimeric oligonucleotides in plants, the reference offers absolutely no guidance or direction for the generation of a chimeric oligonucleotide which would target a specific plant sequence, much less, a herbicide resistance gene or EPSPS as claimed by the present invention.

Moreover, simply the fact that genes for imparting herbicide resistance were known in the art and were used to transform plants (Eichholtz *et al.*, '114 patent ) is no indication that one of skill in the art could have altered a herbicide resistance gene in a plant using a chimeric oligonucleotide and thus be motivated to produce the claimed chimeric oligonucleotides of the present invention. In fact, Eichholtz *et al.* actually teaches away from modifying the EPSPS gene using the chimeric oligonucleotides of the present invention. Specifically, Eichholtz *et al.* ('114 patent) focuses on generating plants transformed with a mutant EPSPS gene. Thus, while the patent provides glyphosate resistant plants, these plant lines are produced by the insertion of the entire mutant EPSPS gene into the plant genome. The resulting plants therefore contain a mutated EPSPS transgene and an endogenous EPSPS sequence. In contrast, the chimeric oligonucleotides of the present invention are not designed to introduce entire transgenes into the genome, but rather are designed to introduce predetermined alterations into the genome. Accordingly, one of skill would not have been motivated to combine the teachings of Kmiec *et al.* ('350 and '972) and Yoon *et al.* with Eichholtz *et al.* to alter herbicide resistance genes in plants, as Eichholtz *et al.* had already provided methods of inserting mutagenized EPSPS genes into plants and thereby rendering them herbicide resistant.

The Examiner is reminded that prior art itself must provide the skilled artisan the motivation to make the required substitution. In the present case, the Examiner has merely used Applicant's claims as a guide and selected secondary references at random that mention various aspects of the claimed invention. This is an improper standard. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988).

The law is clear that without motivation to combine the references, a rejection under 35 USC §103 fails.

The Examiner further asserts that one skilled in the art "would have expected that the transformation of plants (which harbor EPSPS) with chimeric oligonucleotides comprising homologous sequences to EPSPS would introduce desired mutations into the target EPSPS, and subsequently alter the herbicide resistant capabilities of the transformed plants" (page 7, lines 1-4, Office Action mailed April 23, 2002). The art cited by the Examiner does not provide sufficient evidence to warrant this conclusion. Again, the Examiner is reminded that prior to the present invention, successful chimeric oligonucleotide-based gene targeting of herbicide resistance genes had not been reported in plants. Neither Kmiec *et al.* ('350 and '972) nor Yoon *et al.* provide any guidance to one of skill to target herbicide resistance sequences in plants. The instant specification provides the first demonstration of the successful use of chimeric oligonucleotides to introduce alterations in a target herbicide resistance gene in a plant. See Examples 1 and 2. Therefore, prior to the present invention, it was not known that chimeric oligonucleotides could be used to target plant herbicide resistance genes, and consequently, they would not have been motivated to generate the chimeric oligonucleotides claimed by the present invention.

In summary, the Examiner has failed to establish a *prima facie* case of obviousness. As discussed above, there is not a sufficient motivation to combine the teachings of Kmiec *et al.* ('350 and '972) and Yoon *et al.* with Eichholtz *et al.* ('114) to arrive at the claimed invention. Accordingly, Applicants respectfully submit that the claimed chimeric oligonucleotides are not obvious in view of the cited references and respectfully request that the rejection of claims 2-9 and 11 under 35 U.S.C. § 103(a) be withdrawn.

Consideration Of Previously Submitted Information Disclosure Statement

It is noted that an initialed copy of the PTO Form 1449 that was submitted with Applicants' Information Disclosure Statement filed September 22, 2000 has not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed

copy of the Form 1449 be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statement and the Form 1449 are attached hereto. Copies of the cited references were provided at the time of filling the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

CONCLUSIONS

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Kelly J. Williamson
Registration No. 47,179

**Customer No. 29122**
**Alston & Bird LLP**

Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260